Appl. No. 09/100,633
Amdt. dated June 26, 2003
Reply to Office Action of May 21, 2002

REMARKS/ARGUMENTS

The present amendment is submitted in accordance with the Revised Amendment Format as set forth in the Notice provided on the USPTO web site for the Office of Patent Legal Administration; Pre-OG Notices; signed 1/31/03.

Interview of October 4, 2002

The Examiner is thanked for graciously allowing Applicant an interview regarding the above-referenced application.

Status of the Claims

After entry of the amendment, Claims 77-96 are pending. New Claims 91-98 have been added. Claims 79-83 and 85-90 have been amended. Claims 76-78 are canceled without prejudice to renewal.

Claims 79-83 have been amended to correct dependencies in view of new Claim 91.

New Claim 91 replaces canceled Claim 76. Claim 91 recites "a mass spectrometry probe", "docked to a substrate", "binding partner", "in the presence and absence of agent", and "measuring...by laser desorption mass spectrometry." Support for "mass spectrometry probe" is found, for example, at page 29, lines 1-2. Support for "docked to a substrate" is found, for example, at, page 66, lines 27-29, page 65, lines 19-25, and in Figures 14-17. Support for "binding partner" is found, for example, at page 6, lines 19-23. Support for "in the presence and absence of agent" is found, for example, at page 67, lines 5-7. Support for "measuring...by laser desorption mass spectrometry" is found, for example, at page 4, lines 9-11, page 7, lines 26-27, Figure 3 and the corresponding legend on page 14, lines 19-21, page 36, lines 15-21 and in Example XI on page 100, lines 9-10.

Claims 85, 87 and 88 now recite "docked to the substrate." Support is found, for example, at page 66, lines 27-29, page 65, lines 19-25, and in Figures 14-17.

Claim 87 now recites "wherein said receptor or ligand docked to the substrate comprises a fusion protein." Support is found, for example, in Example XI on pages 99-100.

Claim 86 now recites "linker comprises an antibody." Support is found, for example, in Figures 15-17.

Claims 92 and 88 recite "moiety for specific binding." Support is found, for example, at page 65, lines 22-24.

Claims 90 and 93 recite "plurality of agents." Support is found, for example, at page 23, line 3, page 52, lines 27-28, and at page 66, line 25 through page 67, line 2.

Claim 94 recites "screened in parallel." Support is found, for example, at page 52, lines 27-28

Claim 95 recites "bifunctional linker." Support is found, for example, at page 27, line 28 through page 28, line 16.

Claim 96 recites "inhibits binding." Support is found, for example, in Example XI on pages 99-100.

Claim 97 recites "applying a matrix material to the surface before laser desorption mass spectrometry." Claim 98 recites a probe "further comprising energy absorbing molecules chemically bound to the surface before exposing." Support is found, for example on page 25, lines 22-25 where "energy absorbing molecule" is defined; on page 34, line 26 through page 36, line 12, in the section which discusses methods for desorption; and on page 81, line 1 through page 28, line 7, in the section which discusses a protocol for a receptor ligand assay.

Applicants believe no new matter is present with the entry of the newly added claims or amendments, or any other portion of the present amendment. Therefore, Applicants respectfully request that this amendment be entered. Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks.

Rejection under 35 U.S.C. §112, First Paragraph, Written Description Requirement

A. Description of components

The Examiner states that the specification does not adequately describe certain terms in the claims. For the reasons stated below, Applicants respectfully traverse this rejection.

Agent. As the Examiner points out, the term "agent" is defined on page 24, lines 1-6. Agents are also described at length on page 68, line 30 through page 70, line 10 as part 3 of

section K in the specification, which discusses drug discovery. The Examiner objects that the definition for "agent" includes "samples of undetermined composition." Applicants respectfully submit that whether the composition of the agent is determined is not critical to practicing the claimed methods. New Claim 91, the only pending independent claim, is directed to a method of determining whether an agent modulates binding between a receptor/ligand pair that specifically bind to each other. In such a method, that the receptor/ligand pair specifically bind to each other and the conditions that allow binding between the receptor and the ligand are known to those of skill in the art. The method only seeks to determine whether an agent modulates binding between the known receptor/ligand pair. Therefore, any test agent can be screened in the method of Claim 91. The particular character of an agent is not critical to carrying out the claimed invention, which seeks to determine whether receptor/ligand binding is modulated.

Substrate. Substrate is explicitly defined at page 19, lines 14-15 of the specification as referring to a solid phase to which an adsorbent is attached or deposited. New Claim 91 recites "probe comprising a substrate which comprises a receptor or ligand of a receptor/ligand pair docked to the substrate." Support for is found, for example, on page 27, lines 16-27, and on page 29, lines 1-2.

Substrate-bound ligand or receptor. Claims 85, 87, 88, 91 and 92 recite "a receptor or a ligand docked to a (the) substrate." Applicant intends by this language that either a receptor or a ligand of a known receptor/ligand pair can be docked to a substrate. On page 66, lines 27-29, the specification states that "retentate chromatography enables one to dock one member of a ligand/receptor pair to a substrate and to use it as a secondary adsorbent." This is depicted in Figures 14-17 with corresponding legends on page 16, lines 3-26. Binding and retention maps of receptor docked to a substrate is shown in Figures 27 and 33 with corresponding legends on page 18, lines 4-7 and 19-21. Docking of a receptor or ligand to a substrate is further described on page 6, lines 19-23, page 68, lines 8-17, and in Example XI on page 99, line 30 through page 100, line 2. Applicants respectfully submit that "docking" a receptor or ligand to a substrate is the effective equivalent of a substrate-bound receptor or substrate-bound ligand, but have made this amendment in the interest of furthering prosecution.

Small organic molecule. This term, recited in Claim 89, is explicitly defined at page 21, lines 16-19 of the specification to refer to organic molecules of a size comparable to those generally used in pharmaceuticals. As stated on page 21, this term excludes organic biopolymers and preferred small organic molecules range in size up to about 5000 Da. The Examiner points out that the specification recites "small molecules" on page 69, line 1. The sentence referenced by the Examiner states "However, because of their variety and ease of administration as pharmaceuticals, small molecules are preferred as test agents." Applicants respectfully submit, that in the context of this sentence bridging page 68 to 69, which refers to pharmaceuticals, "small molecule" and "small organic molecule," as defined on page 21, are essentially interchangeable.

Linker. Method by which substrate is bound to a linker. The Examiner states that the specification allegedly fails to describe the method by which the substrate is bound to a linker. Applicants respectfully point out that the passage on page 27, line 28 through page 28, line 16 teaches a method of derivatizing a substrate with a bi-functional linker (page 27, lines 28-32) and then further derivatizing the linker with groups that function as the adsorbent, such as a receptor or ligand of a receptor/ligand binding pair (page 28, lines 1-2). Numerous different types of linkers were known to those of skill in the art at the time of filing of the instant application and were commercially available with specific instructions for use (For instance, linkers were readily available through Pierce Biotechnology in Rockford, IL or Sigma-Aldrich Chemical Corp. in St. Louis, MO). Numerous functional groups useful for bi-functional linkers are provided in this passage of the specification. The specification teaches on page 28, lines 11-12 that biopolymers can bind the functional groups through amine residues or sulfhydryl residues. Using an antibody as a linker is depicted in Figures 15-17.

Cell surface receptor. Intracellular receptor. Cell membrane. This language finds support on page 67, lines 28-30 where the specification teaches that the ligand/receptor pair can be a ligand, such as a hormone, and a cell surface receptor or an intracellular receptor. In the case of a membrane-bound receptor, an entire cell or cell membrane can be adsorbed. Additional support is found on page 7, lines 9-12, page 43, lines 15-17, and on page 49, lines 24-26.

Detectable moiety. No claims, as amended, recite this term, which is defined in detail on page 22, lines 12-32.

Combinatorial Library. On page 69, line 5 through page 70, line 10, the section of the specification concerned with the chemistry of test agents for methods of drug discovery discusses combinatorial libraries, including their preparation and screening, at length.

Conditions for the specific interactions. In contrast to the Examiner's assertions, one need not know conditions for specific interactions of different unspecified components to practice the claimed methods. The claimed methods are carried out under conditions that allow specific binding between a known receptor and ligand pair. Conditions that allow binding of a known receptor/ligand pair are already known before practicing the claimed methods, which seek to determine whether an agent modulates the specific binding.

Contrary to the Examiner's assertions, the essential features of the invention, the use of retentate chromatography and detection by laser desorption mass spectrometry is recited in the claims. In new Claim 91, the only independent claim, step a) recites a receptor or ligand docked to a substrate. This language indicates the use of retentate chromatography. As stated above, page 66, lines 27-29, the specification teaches that retentate chromatography enables one to dock one member of a ligand/receptor pair to a substrate and to use it as an adsorbent to specifically bind or capture the binding partner of the docked ligand or receptor. Step b) of Claim 91 explicitly recites measuring an amount of binding by laser desorption mass spectrometry.

B. Allegedly unsupported phrases

Removably insertable. No claims, as amended, recite "probe that is removably insertable" which finds explicit support on page 28, lines 29-30 of the specification.

Bound to substrate through a linker. Amended Claim 85 now recites "docked to the substrate through a linker." As stated above, the passage on page 27, line 28 through page 28, line 16 teaches a method of derivatizing a substrate with a bi-functional linker (page 27, lines 28-32) and then further derivatizing the linker with groups that function as the adsorbent, such as a receptor or ligand of a receptor/ligand binding pair (page 28, lines 1-2).

Fc fragment as a detectable moiety. Claim 87 has been amended to recite "wherein the receptor or ligand docked to the substrate comprises a fusion protein." New Claim

91 recites "wherein the fusion protein further comprises a moiety for specific binding." Claim 88 now depends from Claim 91. Support for these amendments is found, for example, in Figures 27 and 32, on page 18, lines 4-7 and 18; on page 65, lines 22-44; page 68, lines 8-13; and on page 100, lines 1-2.

In view of the foregoing support which conveys possession of the claimed methods at the time of filing of the present application, the Examiner is respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. §112, Second Paragraph

A. Claim 76

Amended Claim 76 does not recite "a screening method." New Claim 92, which depends from Claim 76, recites a screening method of a plurality of agents. Support is found, for example, on page 66, lines 25-27 and in Figure 17.

In accordance with the suggestions of the Examiner, "corresponding" has been amended to recite "binding."

The Examiner states that step c) of canceled Claim 76 is unclear as to what entity is being desorbed and ionized. Step c) of canceled Claim 76 is now step b) of new Claim 91. The Examiner states that retentate chromatography wherein all the components being analyzed are retained on the substrate implies measurement of the components bound to the adsorbent or substrate. Step b) of Claim 91 now recites "measuring...by laser desorption mass spectrometry." Support is found at, for example, page 7, lines 26-27, in Figure 3 and the corresponding legend on page 14, lines 19-21, page 36, lines 15-21 and in Example XI on page 100, lines 9-10.

The language "control amount" has been deleted. In accordance with the Examiner's suggestion, new Claim 91 recites "in the presence and absence of the agent."

The Examiner states that canceled Claim 76 should recite "inhibits" instead of "modulates." "Modulates" is recited in new Claim 91. Applicants respectfully assert that the language "determining whether an agent modulates" is clearly defined in the specification, particularly on page 66, lines 25-27, where the specification teaches that "rapid screening of

combinatorial libraries for drug candidates requires the ability to expose target interactions to thousands of drugs and identify agents that interfere with or promote the interaction. As stated on page 12, lines 20-21, and page 67, lines 5-12, the present methods are concerned with determining the differences in binding of a receptor/ligand pair in the presence and absence of agent. New Claim 96 recites that the agent inhibits binding between a receptor/ligand pair. Support is found in Example XI on page 99, line 30 through page 100, line 22 and schematically in Figures 15-17.

B. Claim 78

Claim 78 has been canceled, thereby obviating the Examiner's objection.

C. Claim 86

Amended Claim 86 explicitly states that the linker is an antibody. Support is found in Figures 15-17, and in their legends on page 16, lines 9-26.

D. Claim 87

Amended Claim 87 recites that the receptor or the ligand docked to the substrate is a fusion protein. Support is found in Example IX, on pages 99-100, and in Figures 27 and 33.

E. Claim 90

Amended Claim 90 depends from Claim 92, directed to screening a plurality of agents, and recites that said plurality of agents comprises a combinatorial library.

F. Claim 89

As stated above, the metes and bounds of what Applicants intend by the term "small organic molecule" is explicitly defined at page 21, lines 16-19 of the specification. As stated on page 21, this term excludes organic biopolymers and preferred small organic molecules range in size up to about 5000 Da. Therefore, Claim 89 can not properly be considered an omnibus claim.

In view of the foregoing amendments and arguments, the Examiner is respectfully requested to withdraw this rejection.

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Rejection under 35 U.S.C. §103(a)

The Examiner has rejected Claims 76-90 under 35 U.S.C. §103(a) as allegedly rendered obvious over Siegel (footnote † on p. 264 of *J. Mass Spectrometry* (1998) 33:264) in view of Kauvar (WO 89/09088).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine the cited references. Second, there must be a reasonable expectation of success. Third, the cited references must teach or suggest all the claim limitations. MPEP § 2143.

Applicants respectfully maintain that the combination of the Siegel abstracts and the Kauvar WO89/09088 does not render the claimed methods obvious because absent impermissible hindsight reconstruction, there is no suggestion or motivation to combine these references, no reasonable expectation of success in the combined methods, and their combination does not disclose every element of the claimed methods.

The Siegel manuscript is not properly cited art

The Siegel manuscript (*J. Mass Spectrometry* (1998) 33:264) was published after the June 20, 1997 effective filing date of the present application, and therefore is not properly cited as prior art. The Examiner cites the Siegel manuscript for the abstracts mentioned in the footnote on page 264 ("the Siegel abstracts"), in particular:

> Siegel, *et al.*, "Inhibition Mechanisms and Kinetics of Human Cytomegalovirus Protease Inhibitors Analyzed by ESI/MS", **Abstract No. 1424**, 44th ASMS Conference, May 12-16 (1996).
>
> Siegel, *et al.*, "A Rapid Method for Screening Low Molecular Mass Compounds Non-covalently Bound to Proteins Using Size Exclusion and Mass Spectrometry Applied to Inhibitors of Human Cytomegalovirus Protease", **Abstract No. 907**, 45th ASMS Conference, June 1-5 (1997).

Because it is not prior art, the Examiner cannot use the Siegel manuscript to find that the present invention is anticipated or obvious. According to the Examiner, the Siegel

abstracts were, apparently, published before the priority date of this application. Copies of the Siegel abstracts are provided in an IDS filed concurrently herewith in a separate paper. Accordingly, Applicants respond to this rejection by addressing the disclosure in the above-referenced Siegel abstracts.

Siegel and Kauvar do ***not*** disclose or suggest all claim elements

The claimed method comprises the following five steps: (1) docking of a receptor/ligand to the surface of a mass spectrometry probe; (2) exposing the docked molecule to its binding partner and an agent; (3) removing unbound binding partner; (4) measuring the amount of binding by laser desorption mass spectrometry from the probe surface; and (5) comparing the amount of binding between the binding pair in the presence and absence of the agent to determine whether the agent modulated binding. None of the cited documents, alone or in combination, disclose all of these steps. Nor is there any suggestion in any of the documents to provide the missing steps. Therefore, the cited references do ***not*** render the invention obvious.

Neither Kauver nor Siegel disclose or suggest docking a member of a receptor/ligand pair to the surface of a mass spectrometry probe. The Siegel methods are performed in solution. Kauver discusses attaching molecules to a substrate, but nowhere in Kauver are the substrates described as mass spectrometry probes or suggested for that purpose.

Neither Kauver nor Siegel suggest performing a capture step on the surface of a mass spectrometry probe. Siegel refers to binding between enzymes and enzyme inhibitors in solution. Kauver refers to binding between "paralogs" and other molecules, such as proteins, on a substrate, but not on a mass spectrometry probe.

Neither Kauver nor Siegel disclose or suggest detection of binding between two molecules docked on a mass spectrometry probe by laser desorption mass spectrometry from the surface of the probe. Kauver refers to labeling the molecule to be captured, and detecting capture by detecting the label. Siegel refers to subjecting the enzyme-inhibitor complex to electrospray mass spectrometry. Electrospray mass spectrometry involves spraying a liquid comprising the analyte into a mass spectrometer for subsequent detection. Electrospray does not involve the use of mass spectrometry probes and, indeed, is incompatable with it, because one

cannot spray a substance bound to a mass spectrometry probe. If a proposed modification to a cited reference would render that reference unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. Accordingly, neither Kauver nor Siegel disclose or suggest detection by laser desorption of the substrate and detection by mass spectrometry.

No expectation of success

Because Siegel's protease/inhibitor detection methods wholly depend on the different electrospray ionization mass spectrometry profiles between eluants containing unbound protease and protease/inhibitor complexes, one of skill in the art would have no reasonable expectation of success by combining the method of the Siegel abstracts with the affinity chromatography methods of Kauvar.

Because the combined disclosures of the Siegel abstracts and the Kauvar PCT application do not properly render the claimed methods obvious, the Examiner is respectfully requested to withdraw this rejection.

PATENT

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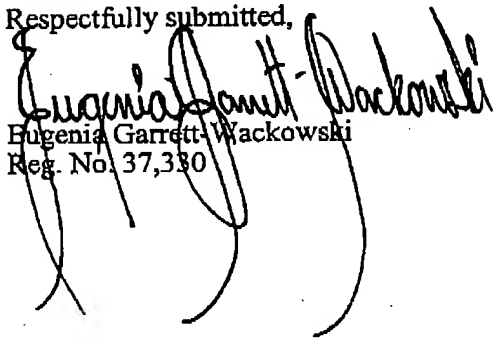
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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